F ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 February 2001 (06.02.01)	
International application No. PCT/GB00/02085	**Applicant's or agent's file reference** PHM.70554/WO
International filing date (day/month/year) 31 May 2000 (31.05.00)	**Priority date** (day/month/year) 04 June 1999 (04.06.99)
Applicant TUCKER, Howard	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 December 2000 (18.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Christine Carrié
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

PHILIPS, Neil, Godfrey, Alasdair
AstraZeneca
P.O. Box 272
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG
ROYAUME-UNI

Date of mailing (day/month/year)
06 February 2001 (06.02.01)

Applicant's or agent's file reference
PHM.70554/WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/02085

International filing date (day/month/year)
31 May 2000 (31.05.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN, United Kingdom
ZENECA-PHARMA S.A.
Le Galien
1, rue des Chauffours, BP 127
F-95022 Cergy Cédex, France

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
ASTRAZENECA AB
S-151 85 Södertalje
Sweden

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Christine Carrié

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

003819470

PCT/GB00/02085

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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

PHILIPS, Neil, Godfrey, Alasdair
AstraZeneca
P.O. Box 272
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG
ROYAUME-UNI

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Applicant's or agent's file reference PHM.70554/WO	**IMPORTANT NOTIFICATION**
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1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address

* ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN, United Kingdom
* ZENECA-PHARMA S.A.
Le Galien
1, rue des Chauffours, BP 127
F-95022 Cergy Cédex, France

State of Nationality	State of Residence
GB	GB

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address

ASTRAZENECA AB
S-151 85 Södertalje
Sweden

CODE	DATE	NTD

REC'D 12 FEB 2001 GIPS

DATA ENTERED

FINAL CHECK

State of Nationality	State of Residence
GB	GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer C. CARRÉ Christine Carrié
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

003819470

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PHM.70554/WO

Box No. I TITLE OF INVENTION

COMPOUNDS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ASTRAZENECA UK LIMITED
15 Stanhope Gate
London
W1Y 6LN
GB

☐ This person is also inventor.

Telephone No.
(01625) 516173

Facsimile No.
(01625) 583358

Teleprinter No.
669095/669388

State *(that is, country)* of nationality:
GB

State *(that is, country)* of residence:
GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ZENECA-PHARMA S.A.
'Le Galien'
1 rue des Chauffours, BP 127
95022 Cergy Cedex
FR

This person is:

☒ applicant only

☐ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:
FR

State *(that is, country)* of residence:
FR

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ASTRAZENECA
P O Box 272
Mereside, Alderley Park
Macclesfield, Cheshire, SK10 4TG
GB

Telephone No.
(01625) 514620

Facsimile No.
(01625) 583358

Teleprinter No.
669095/669388

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURT[illegible]APPLICANT(S) AND/OR (FURTHER) INVE[illegible]R(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TUCKER, Howard
Alderley Park
Macclesfield
Cheshire, SK10 4TG
GB

This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AE** United Arab Emirates
☒ **AL** Albania
☒ **AM** Armenia
☒ **AT** Austria
☒ **AU** Australia
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina
☒ **BB** Barbados
☒ **BG** Bulgaria
☒ **BR** Brazil
☒ **BY** Belarus
☒ **CA** Canada
☒ **CH and LI** Switzerland and Liechtenstein
☒ **CN** China
☒ **CR** Costa Rica
☒ **CU** Cuba
☒ **CZ** Czech Republic
☒ **DE** Germany
☒ **DK** Denmark
☒ **DM** Dominica
☒ **EE** Estonia
☒ **ES** Spain
☒ **FI** Finland
☒ **GB** United Kingdom
☒ **GD** Grenada
☒ **GE** Georgia
☒ **GH** Ghana
☒ **GM** Gambia
☒ **HR** Croatia
☒ **HU** Hungary
☒ **ID** Indonesia
☒ **IL** Israel
☒ **IN** India
☒ **IS** Iceland
☒ **JP** Japan
☒ **KE** Kenya
☒ **KG** Kyrgyzstan
☒ **KP** Democratic People's Republic of Korea
☒ **KR** Republic of Korea
☒ **KZ** Kazakhstan
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MA** Morocco
☒ **MD** Republic of Moldova
☒ **MG** Madagascar
☒ **MK** The former Yugoslav Republic of Macedonia
☒ **MN** Mongolia
☒ **MW** Malawi
☒ **MX** Mexico
☒ **NO** Norway
☒ **NZ** New Zealand
☒ **PL** Poland
☒ **PT** Portugal
☒ **RO** Romania
☒ **RU** Russian Federation
☒ **SD** Sudan
☒ **SE** Sweden
☒ **SG** Singapore
☒ **SI** Slovenia
☒ **SK** Slovakia
☒ **SL** Sierra Leone
☒ **TJ** Tajikistan
☒ **TM** Turkmenistan
☒ **TR** Turkey
☒ **TT** Trinidad and Tobago
☒ **TZ** United Republic of Tanzania
☒ **UA** Ukraine
☒ **UG** Uganda
☒ **US** United States of America
☒ **UZ** Uzbekistan
☒ **VN** Viet Nam
☒ **YU** Yugoslavia
☒ **ZA** South Africa
☒ **ZW** Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ DZ Algeria
☒ AG Antigua

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims [redacted]icated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 04 June 1999 (04.06.99)	99401350.6	EP		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* :

ISA / EPO

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request	: 4
description (excluding sequence listing part)	: 26
claims	: 7
abstract	: 1
drawings	:
sequence listing part of description	:
Total number of sheets	: 34

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s): (1)
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

PHILLIPS, Neil Godfrey Alasdair et al.

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PHM.70554/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02085	31/05/2000	04/06/1999
International Patent Classification (IPC) or national classification and IPC C07D211/28		
Applicant ASTRAZENECA AB & AL.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/12/2000	05.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Feiler, L Telephone No. +49 89 2399 8282

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02085

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-26 as originally filed

Claims, No.:

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1, 4-12.

because:

☒ the said international application, or the said claims Nos. 8 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1, 4-7, 9-12.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 2, 3
	No:	Claims
Inventive step (IS)	Yes:	Claims
	No:	Claims 2, 3
Industrial applicability (IA)	Yes:	Claims 2, 3
	No:	Claims

2. Citations and explanations
   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Claim 8 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
Since the Search Report cannot be considered to be complete the following observations apply to subject matter of Claims 2 and 3 only.

2. Cited Documents

WO-A-9902510= D1
US-A-5817822= D2
DE-A-19802350= D3
WO-A-9918074= D4
WO-A-0012478= D5
WO-A-9938843= D6
The indicated designation will be used throughout the examination procedure.
D5 and D6 are P-documents.

3. Novelty

The subject-matter of Claim 2 is comprised by D1 but may be considered to be a novel selection therefrom since D1 appears to disclose no specific compounds or groups of compounds falling within Claim 2. Subject matter of Claim 2 differs essentially from D2 in that the A-ring corresponding moiety is according to D2 a phenyl ring not considered according to the application.
Subject matter of Claim 3 differs from D1, D2 and D3 due to the fact that Z is -N(OH)CHO according to Claim 3 of the application not considered according to D1, D2 and D3.
Subject matter of Claim 2 differs from D3 essentially due to the fact that according to D3 a moiety corresponding to ring B is not present according to D3.
D4 differs from subject matter of Claims 2 and 3 essentially due to the fact that this prior art discloses a lactam moiety not considered according to Claims 2 and 3 of the applcation.
The compounds of D6 differ from subject matter of Claims 2 and 3 essentialy in that the D6-compounds do not comprise a moiety corresponding to the A-ring of the Claims 2

and 3 according to the application.
On the other hand D5 discloses compounds (see e.g. compounds on page 42 of D5) which fall within subject matter of Claims 2 and 3.
If the claimed priority date is valid D5 and D6 may at present remain outside consideration but specifically D5 will be highly relevant in a possible national or regional examination phase. Since the priority documents have not reached the examination file it is at present not possible to check the validity of the claimed priority date 04/06/99.
The subject-matter of Claims 2 and 3 can therefore be considered novel.

4. Inventive Step - Breadth of Claims - Non-unity a posteriori

4.1 Subjective Problem
According to the application (p. 1, first and third paragraph; page 9, lines 8-15) the problem underlying the invention is to be seen in the provision of compounds which inhibit specific matrix metalloproteinases (MMP) namely which inhibit selectively MMP13 and which inter alia are able to inhibit the tumour necrosis factor (TNF).
4.2 Relevant and closest prior art
Documents D1-D4 are considered to be relevant for the assessment of inventive step since the compounds disclosed therein come structurally close to the subject matter of Claims 2 and 3 and also appear to have the same property at least qualitatively.
For **invention A** according to Claim 2 wherein Z= -CONHOH the closest prior art is given by D1.
For **invention B** according to Claims 2 and 3 wherein Z= -N(OH)CHO the closest prior art is given by D4.
If the claimed priority date is not justifiable D5 is highly relevant for inventive step considerations.
4.3 Objectively solved problem
The application documents contain insufficient information (the test methodology is disclosed but no quantitative test data or comparative test data are given) upon which a judgement as to whether the technical problem according to point 4.1 has actually been solved or not by the claimed products it may be considered in view of the cited prior art credible that the technical problem indicated above is, at least partially, solved by the prepared compounds. In view of the cited prior art it can only be said that the problem which has actually been solved is to provide further compounds which are inhibitors of matrix metalloproteinases.

4.4 Evaluation of the solution of the problem
D1-D4 disclose compounds structurally very similar to those of the present application. The products of those documents also solve the problem of providing compounds which are inhibitors of matrix metalloproteinases.
The person skilled in the art seeking a solution to the problem defined above would therefore have been prompted to consider further derivatives of compounds which are already known to solve the above defined problem. In this context it is to be stressed that the compounds of the cited prior art show a wide variation of possibilities to solve the problem indicated in point 4.3.
From an overall view of the teachings of D1-D4 and specifically from D1 and D4 the person skilled in the art would have been able to infer that a modification of proposed type would have no effect on the activity profile.
The person skilled in the art would therefore have considered the proposed solution in the expectation of success.
The solution of the technical problem defined in point 4.3 according to the application is therefore obvious in the light of the prior art. Thus the subject-matter of the present Claim 1 cannot be considered to be inventive.
4.5 As indicated, D1 and D4 are considered as the closest prior art depending on the structure of the compounds claimed. Consequently, two different problems are to be solved and therefore subject matter claimed must be considered to be non-unitary.

5. Industrial applicability

For the assessment of the present claim 8 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6. Clarity

Claims 2 and 3 contain unclear matter.
- A is defined as aliphatic ring but in fact X_1 and X_2 are N.

- The expression "in vivo hydrolysable precurser" is unclear in structure and therefore not acceptable.
- The set of claims comprises independent product claims.
- There is lack of concisesness of the claims since repetition of substituents has not been avoided by corresponding references to previous claims.

7. Suggestions

In a possible national or regional examination phase an inventive step could nevertheless be acknowledged should comparative data be submitted which show that apart from the technical problem defined in point 4.1 another, possibly more exacting, problem, which can be derived from the application as originally filed (e.g. surprising improvement), existed and has actually been solved by originally disclosed technical features, which would need to be incorporated in the claims.
In this respect it should be borne in mind that the compounds of the closest prior art D1 and D4 must bear the closest possible structural resemblance in order that the comparison be valid.
The breadth of Claim 1 should be such that it can be assumed that all the comprised possibilities actually solve the problem underlying the invention on which an inventive step could be based.
It is apparent that the compounds which have been prepared have the following characteristics:
Ring A= 1,4-piperazinyl;
P= bond;
Ring B= 4-F-phenyl;
Y= SO_2;
Q= CH_2;
Z= -N(OH)CHO;
R^1= H;
R^2= 4-piperidinyl.
If those possibilities are essential to the activity on which an inventive step could be based the claims should be restricted accordingly whereby **reasonable** generalisations are acceptable. Expressions like "heteroalkylring" or "alkyl" etc. with an undefined C-range are certainly not a reasonable generalisation.

The description should be adapted to the new claims in the framework of the original disclosure.

Any examples and parts of the description no longer encompassed by Claim 1 are to be deleted.

The documents cited in this communication should, insofar as this has not taken place, be referred to in the description with a short indication of their contents.

Pages amended in handwriting should also be submitted retyped.

P NT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PHM.70554/WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 02085	31/05/2000	04/06/1999
Applicant		
ASTRAZENECA UK LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

INHIBITORS OF METALLOPROTEINASES

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,4-12 (all partially)

Present claims 1,4-12 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I, in which Z is -CONHOH, -N(OH)CHO or -N(OH)COR.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 00/02085

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/28 C07D401/12 C07D409/12 A61K31/445 A61K31/4535 A61P19/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 02510 A (BISSOLINO PIERLUIGI ;JABES DANIELA (IT); ALPEGIANI MARCO (IT); PER) 21 January 1999 (1999-01-21) claim 1; examples	1-12
A	US 5 817 822 A (MACPHERSON LAWRENCE J ET AL) 6 October 1998 (1998-10-06) claim 1	1-12
A	DE 198 02 350 A (HOFFMANN LA ROCHE ;AGOURON PHARMA (US)) 30 July 1998 (1998-07-30) claim 1; examples	1-12
A	WO 99 18074 A (DU PONT PHARM CO) 15 April 1999 (1999-04-15) claim 1; examples	1-12

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2000	24/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 00/02085

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 12478 A (ZENECA PHARMA SA ;TUCKER HOWARD (GB); WATERSON DAVID (GB); ZENECA) 9 March 2000 (2000-03-09) compound in which R1 is N-PhCH2-4-piperidinyl page 42 ---	1-12
P,X	WO 99 38843 A (DARWIN DISCOVERY LTD) 5 August 1999 (1999-08-05) claims; examples -----	1,6-8, 10-12

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT [redacted] 00/02085

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9902510 A	21-01-1999	AU 8858398 A	08-02-1999
		EP 0925289 A	30-06-1999
US 5817822 A	06-10-1998	US 5646167 A	08-07-1997
		US 5552419 A	03-09-1996
		US 5506242 A	09-04-1996
		AU 6124996 A	30-12-1996
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		US 5672615 A	30-09-1997
		AT 196762 T	15-10-2000
		AU 692553 B	11-06-1998
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		ZA 9505206 A	27-12-1995
DE 19802350 A	30-07-1998	AU 6614098 A	18-08-1998
		BG 103586 A	31-03-2000
		BR 9807508 A	21-03-2000
		CN 1250445 T	12-04-2000
		WO 9832748 A	30-07-1998
		EP 0958287 A	24-11-1999
		ES 2136037 A	01-11-1999
		FR 2758559 A	24-07-1998
		GB 2321641 A	05-08-1998
		HR 980036 A	31-12-1998
		IT MI980091 A	23-07-1998
		NO 993587 A	22-09-1999
		PL 334846 A	27-03-2000
		US 5998412 A	07-12-1999
		ZA 9800376 A	23-07-1998
		US 6130220 A	10-10-2000
WO 9918074 A	15-04-1999	AU 9686698 A	27-04-1999
		EP 1027332 A	16-08-2000
		HR 980533 A	31-10-1999
		NO 20000783 A	29-05-2000
		US 6057336 A	02-05-2000
WO 0012478 A	09-03-2000	AU 5524799 A	21-03-2000
WO 9938843 A	05-08-1999	AU 2291499 A	16-08-1999
		NO 20003868 A	28-07-2000

DO/ EO WORKSHEET

U.S. Appl. No. _____ International Appl. No. _____

Application filed by : ☐ 20 months ☐ 30 months

WIPO PUBLICATION INFORMATION :

Publication No.: WO 00/ 75108 Publication Language : ☐ English ☐ Japanese ☐ German ☐ French ☐ Other : _____ Screening Done by :

Publication Date : 14 Dec 2000 Not Published : ☐ U.S. only designated ☐ EP request

INTERNATIONAL APPLICATION PAPERS IN THE APPLICATION FILE :

- ☐ International Application *(RECORD COPY)*
- ☐ Article 19 Amendments
- ☐ PCT/IB/331
- ☐ PCT/IPEA/409 IPER (PCT/IPEA/416 on front)
- ☐ Annexes to 409
- ☐ Priority Document (s) No. _____
- ☐ International Appl. on Double Sided Paper *(COPIES MADE)*
- ☐ Request form PCT/RO/101
- ☐ PCT/ISA/210 - Search Report
- ☐ Search Report References
- ☐ Other : _____

RECEIPTS FROM THE APPLICANT *(other than checked above) :*

- ☐ Basic National Fee (*or authorization to charge*)
- ☐ Description
- ☐ Claims
- ☐ Words in the Drawing Figure(s)
- ☐ Article 19 Amendments
  - ☐ english transl. of annexes NOT present
  - ☐ entered ☐ not entered :
    - ☐ not a page for page substitution
    - ☐ other : _____
- ☐ Annexes to 409
  - ☐ english transl. of annexes NOT present
  - ☐ entered ☐ not entered :
    - ☐ not a page for page substitution
    - ☐ other : _____
- ☐ Preliminary Amendment(s) Filed on : 1. _____ 2. _____ 3. _____
- ☐ Information Disclosure Statement(s) Filed on : 1. _____ 2. _____ 3. _____
- ☐ Assignment Document
- ☐ Power of Attorney/ Change of Address
- ☐ Substitute Specification Filed on : 1. _____ 2. _____
- ☐ Verified Small Status Statement (executed)
- ☐ Oath/ Declaration (executed)
  - ☐ surcharge was paid at the time of filing
- ☐ DNA Diskette
- ☐ Other : 1. _____ 2. _____

NOTES : ☐ I.A. used as Specification ☐ Other :

35 U.S.C. 371 - Receipt of Request (PTO-1390)
Date Acceptable Oath/ Declaration Received
Date of Completion of requirements under 35 U.S.C. 371
102(e) Date
Date of Completion of DO/ EO 906 - Notification of Missing 102(e) Requirements
Date of Completion of DO/ EO 907 - Notification of Acceptance for 102(e) Date
Date of Completion of DO/ EO 911 - Application Accepted Under 35 U.S.C. 111
Date of Completion of DO/ EO 905 - Notification of Missing Requirements
Date f Completion of DO/ EO 916 - Notification f Defective Response
Date of Completion of DO/ EO 903 - Notification f Acceptance
Date f Completion of DO/ EO 909 - Notification f Abandonment

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[redacted] 00/02085

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/28 C07D401/12 C07D409/12 A61K31/445 A61K31/4535 A61P19/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 5 817 822 A (MACPHERSON LAWRENCE J ET AL) 6 October 1998 (1998-10-06) claim 1	1-12
A	DE 198 02 350 A (HOFFMANN LA ROCHE ;AGOURON PHARMA (US)) 30 July 1998 (1998-07-30) claim 1; examples	1-12
A	WO 99 18074 A (DU PONT PHARM CO) 15 April 1999 (1999-04-15) claim 1; examples	1-12

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2000	24/11/2000

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL – 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 00/02085

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 12478 A (ZENECA PHARMA SA ;TUCKER HOWARD (GB); WATERSON DAVID (GB); ZENECA) 9 March 2000 (2000-03-09) compound in which R1 is N-PhCH2-4-piperidinyl page 42	1-12
P,X	WO 99 38843 A (DARWIN DISCOVERY LTD) 5 August 1999 (1999-08-05) claims; examples	1,6-8, 10-12

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information [redacted] patent family members

International Application No
PCT/[redacted]00/02085

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9902510 A	21-01-1999	AU 8858398 A	08-02-1999
		EP 0925289 A	30-06-1999
US 5817822 A	06-10-1998	US 5646167 A	08-07-1997
		US 5552419 A	03-09-1996
		US 5506242 A	09-04-1996
		AU 6124996 A	30-12-1996
		WO 9640101 A	19-12-1996
		US 5672615 A	30-09-1997
		AT 196762 T	15-10-2000
		AU 692553 B	11-06-1998
		AU 2536995 A	19-01-1996
		CA 2192092 A	04-01-1996
		DE 69519024 D	09-11-2000
		EP 0766672 A	09-04-1997
		FI 965156 A	20-12-1996
		HU 76548 A	29-09-1997
		WO 9600214 A	04-01-1996
		JP 11505502 T	21-05-1999
		NO 965568 A	17-02-1997
		ZA 9505206 A	27-12-1995
DE 19802350 A	30-07-1998	AU 6614098 A	18-08-1998
		BG 103586 A	31-03-2000
		BR 9807508 A	21-03-2000
		CN 1250445 T	12-04-2000
		WO 9832748 A	30-07-1998
		EP 0958287 A	24-11-1999
		ES 2136037 A	01-11-1999
		FR 2758559 A	24-07-1998
		GB 2321641 A	05-08-1998
		HR 980036 A	31-12-1998
		IT MI980091 A	23-07-1998
		NO 993587 A	22-09-1999
		PL 334846 A	27-03-2000
		US 5998412 A	07-12-1999
		ZA 9800376 A	23-07-1998
		US 6130220 A	10-10-2000
WO 9918074 A	15-04-1999	AU 9686698 A	27-04-1999
		EP 1027332 A	16-08-2000
		HR 980533 A	31-10-1999
		NO 20000783 A	29-05-2000
		US 6057336 A	02-05-2000
WO 0012478 A	09-03-2000	AU 5524799 A	21-03-2000
WO 9938843 A	05-08-1999	AU 2291499 A	16-08-1999
		NO 20003868 A	28-07-2000

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PHM.70554/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02085	31/05/2000	04/06/1999
International Patent Classification (IPC) or national classification and IPC C07D211/28		
Applicant ASTRAZENECA AB & AL.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/12/2000	05.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Feiler, L Telephone No. +49 89 2399 8282

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02085

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-26 as originally filed

Claims, No.:

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1, 4-12.

because:

☒ the said international application, or the said claims Nos. 8 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1, 4-7, 9-12.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2, 3
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	2, 3
Industrial applicability (IA)	Yes:	Claims	2, 3
	No:	Claims	

2. Citations and explanations
   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Claim 8 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
Since the Search Report cannot be considered to be complete the following observations apply to subject matter of Claims 2 and 3 only.

2. Cited Documents

WO-A-9902510= D1
US-A-5817822= D2
DE-A-19802350= D3
WO-A-9918074= D4
WO-A-0012478= D5
WO-A-9938843= D6
The indicated designation will be used throughout the examination procedure.
D5 and D6 are P-documents.

3. Novelty

The subject-matter of Claim 2 is comprised by D1 but may be considered to be a novel selection therefrom since D1 appears to disclose no specific compounds or groups of compounds falling within Claim 2. Subject matter of Claim 2 differs essentially from D2 in that the A-ring corresponding moiety is according to D2 a phenyl ring not considered according to the application.
Subject matter of Claim 3 differs from D1, D2 and D3 due to the fact that Z is -N(OH)CHO according to Claim 3 of the application not considered according to D1, D2 and D3.
Subject matter of Claim 2 differs from D3 essentially due to the fact that according to D3 a moiety corresponding to ring B is not present according to D3.
D4 differs from subject matter of Claims 2 and 3 essentially due to the fact that this prior art discloses a lactam moiety not considered according to Claims 2 and 3 of the applcation.
The compounds of D6 differ from subject matter of Claims 2 and 3 essentialy in that the D6-compounds do not comprise a moiety corresponding to the A-ring of the Claims 2

and 3 according to the application.
On the other hand D5 discloses compounds (see e.g. compounds on page 42 of D5) which fall within subject matter of Claims 2 and 3.
If the claimed priority date is valid D5 and D6 may at present remain outside consideration but specifically D5 will be highly relevant in a possible national or regional examination phase. Since the priority documents have not reached the examination file it is at present not possible to check the validity of the claimed priority date 04/06/99.
The subject-matter of Claims 2 and 3 can therefore be considered novel.

4. Inventive Step - Breadth of Claims - Non-unity a posteriori

4.1 Subjective Problem
According to the application (p. 1, first and third paragraph; page 9, lines 8-15) the problem underlying the invention is to be seen in the provision of compounds which inhibit specific matrix metalloproteinases (MMP) namely which inhibit selectively MMP13 and which inter alia are able to inhibit the tumour necrosis factor (TNF).
4.2 Relevant and closest prior art
Documents D1-D4 are considered to be relevant for the assessment of inventive step since the compounds disclosed therein come structurally close to the subject matter of Claims 2 and 3 and also appear to have the same property at least qualitatively.
For **invention A** according to Claim 2 wherein Z= -CONHOH the closest prior art is given by D1.
For **invention B** according to Claims 2 and 3 wherein Z= -N(OH)CHO the closest prior art is given by D4.
If the claimed priority date is not justifiable D5 is highly relevant for inventive step considerations.
4.3 Objectively solved problem
The application documents contain insufficient information (the test methodology is disclosed but no quantitative test data or comparative test data are given) upon which a judgement as to whether the technical problem according to point 4.1 has actually been solved or not by the claimed products it may be considered in view of the cited prior art credible that the technical problem indicated above is, at least partially, solved by the prepared compounds. In view of the cited prior art it can only be said that the problem which has actually been solved is to provide further compounds which are inhibitors of matrix metalloproteinases.

4.4 Evaluation of the solution of the problem
D1-D4 disclose compounds structurally very similar to those of the present application. The products of those documents also solve the problem of providing compounds which are inhibitors of matrix metalloproteinases.
The person skilled in the art seeking a solution to the problem defined above would therefore have been prompted to consider further derivatives of compounds which are already known to solve the above defined problem. In this context it is to be stressed that the compounds of the cited prior art show a wide variation of possibilities to solve the problem indicated in point 4.3.
From an overall view of the teachings of D1-D4 and specifically from D1 and D4 the person skilled in the art would have been able to infer that a modification of proposed type would have no effect on the activity profile.
The person skilled in the art would therefore have considered the proposed solution in the expectation of success.
The solution of the technical problem defined in point 4.3 according to the application is therefore obvious in the light of the prior art. Thus the subject-matter of the present Claim 1 cannot be considered to be inventive.
4.5 As indicated, D1 and D4 are considered as the closest prior art depending on the structure of the compounds claimed. Consequently, two different problems are to be solved and therefore subject matter claimed must be considered to be non-unitary.

5. Industrial applicability

For the assessment of the present claim 8 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6. Clarity

Claims 2 and 3 contain unclear matter.
- A is defined as aliphatic ring but in fact X_1 and X_2 are N.

- The expression "in vivo hydrolysable precurser" is unclear in structure and therefore not acceptable.
- The set of claims comprises independent product claims.
- There is lack of concisesness of the claims since repetition of substituents has not been avoided by corresponding references to previous claims.

7. Suggestions

In a possible national or regional examination phase an inventive step could nevertheless be acknowledged should comparative data be submitted which show that apart from the technical problem defined in point 4.1 another, possibly more exacting, problem, which can be derived from the application as originally filed (e.g. surprising improvement), existed and has actually been solved by originally disclosed technical features, which would need to be incorporated in the claims.
In this respect it should be borne in mind that the compounds of the closest prior art D1 and D4 must bear the closest possible structural resemblance in order that the comparison be valid.
The breadth of Claim 1 should be such that it can be assumed that all the comprised possibilities actually solve the problem underlying the invention on which an inventive step could be based.
It is apparent that the compounds which have been prepared have the following characteristics:
Ring A= 1,4-piperazinyl;
P= bond;
Ring B= 4-F-phenyl;
Y= SO_2;
Q= CH_2;
Z= -N(OH)CHO;
R^1= H;
R^2= 4-piperidinyl.
If those possibilities are essential to the activity on which an inventive step could be based the claims should be restricted accordingly whereby **reasonable** generalisations are acceptable. Expressions like "heteroalkylring" or "alkyl" etc. with an undefined C-range are certainly not a reasonable generalisation.

The description should be adapted to the new claims in the framework of the original disclosure.

Any examples and parts of the description no longer encompassed by Claim 1 are to be deleted.

The documents cited in this communication should, insofar as this has not taken place, be referred to in the description with a short indication of their contents.

Pages amended in handwriting should also be submitted retyped.

INHIBITORS OF METALLOPROTEINASES

The present invention relates to compounds useful in the inhibition of metalloproteinases and in particular to pharmaceutical compositions comprising these, as well as their use.

The compounds of this invention are inhibitors of one or more metalloproteinase enzymes. Metalloproteinases are a superfamily of proteinases (enzymes) whose numbers in recent years have increased dramatically. Based on structural and functional considerations these enzymes have been classified into families and subfamilies as described in N. M Hooper (1994) FEBS Letters 354:1-6. Examples of metalloproteinases include the matrix metalloproteinases (MMP) such as the collagenases (MMP1, MMP8, MMP13), the gelatinases (MMP2, MMP9), the stromelysins (MMP3, MMP10, MMP11), matrilysin (MMP7), metalloelastase (MMP12), enamelysin (MMP19), the MT-MMPs (MMP14, MMP15, MMP16, MMP17); the reprolysin or adamalysin or MDC family which includes the secretases and sheddases such as TNF converting enzymes (ADAM10 and TACE); the astacin family which include enzymes such as procollagen processing proteinase (PCP); and other metalloproteinases such as aggrecanase, the endothelin converting enzyme family and the angiotensin converting enzyme family.

Metalloproteinases are believed to be important in a plethora of physiological disease processes that involve tissue remodelling such as embryonic development, bone formation and uterine remodelling during menstruation. This is based on the ability of the metalloproteinases to cleave a broad range of matrix substrates such as collagen, proteoglycan and fibronectin. Metalloproteinases are also believed to be important in the processing, or secretion, of biological important cell mediators, such as tumour necrosis factor (TNF); and the post translational proteolysis processing, or shedding, of biologically important membrane proteins, such as the low affinity IgE receptor CD23 (for a more complete list see N. M. Hooper *et al.*, (1997) Biochem J. 321:265-279).

Metalloproteinases have been associated with many disease conditions. Inhibition of the activity of one or more metalloproteinases may well be of benefit in these disease conditions, for example: various inflammatory and allergic diseases such as, inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis), inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or

invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease)); in diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); Alzheimer's disease; and extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atheroscelerosis.

A number of metalloproteinase inhibitors are known; different classes of compounds may have different degrees of potency and selectivity for inhibiting various metalloproteinases. We have discovered a new class of compounds that are inhibitors of metalloproteinases and are of particular interest in inhibiting MMP-13. The compounds of this invention have beneficial potency and/or pharmacokinetic properties.

MMP13, or collagenase 3, was initially cloned from a cDNA library derived from a breast tumour [J. M. P. Freije *et al.* (1994) Journal of Biological Chemistry 269(24):16766-16773]. PCR-RNA analysis of RNAs from a wide range of tissues indicated that MMP13 expression was limited to breast carcinomas as it was not found in breast fibroadenomas, normal or resting mammary gland, placenta, liver, ovary, uterus, prostate or parotid gland or in breast cancer cell lines (T47-D, MCF-7 and ZR75-1). Subsequent to this observation MMP13 has been detected in transformed epidermal keratinocytes [N. Johansson *et al.*, (1997) Cell Growth Differ. 8(2):243-250], squamous cell carcinomas [N. Johansson *et al.*, (1997) Am. J. Pathol. *151(2)*:499-508] and epidermal tumours [K. Airola *et al.*, (1997) J. Invest. Dermatol. *109(2)*:225-231]. These results are suggestive that MMP13 is secreted by transformed epithelial cells and may be involved in the extracellular matrix degradation and cell-matrix interaction associated with metastasis especially as observed in invasive breast cancer lesions and in malignant epithelia growth in skin carcinogenesis.

Recent published data implies that MMP13 plays a role in the turnover of other connective tissues. For instance, consistent with MMP13's substrate specificity and preferential to degrade type II collagen [P. G. Mitchell *et al.*, (1996) J. Clin. Invest. *97(3)*:761-768; V. Knauper *et al.*, (1996) The Biochemical Journal 271:1544-1550], MMP13 has been hypothesised to serve a role during primary ossification and skeletal remodelling [M. Stahle-Backdahl *et al.*, (1997) Lab. Invest. 76(5):717-728; N. Johansson *et al.*, (1997) Dev. Dyn. 208(3):387-397], in destructive joint diseases such as rheumatoid and osteo-arthritis [D.

Wernicke *et al.*, (1996) J. Rheumatol. 23:590-595; P. G. Mitchell et al., (1996) J. Clin. Invest. 97(3):761-768; O. Lindy *et al.*, (1997) Arthritis Rheum 40(8):1391-1399]; and during the aseptic loosening of hip replacements [S. Imai *et al.*, (1998) J. Bone Joint Surg. Br. 80(4):701-710]. MMP13 has also been implicated in chronic adult periodontitis as it has been localised to the epithelium of chronically inflamed mucosa human gingival tissue [V. J. Uitto *et al.*, (1998) Am. J. Pathol 152(6):1489-1499] and in remodelling of the collagenous matrix in chronic wounds [M. Vaalamo *et al.*, (1997) J. Invest. Dermatol. 109(1):96-101].

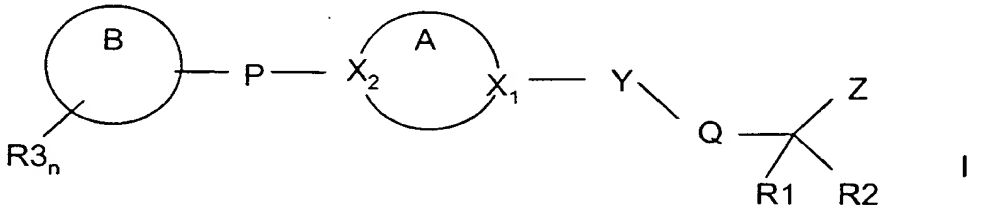
MMP9 (Gelatinase B; 92kDa TypeIV Collagenase; 92kDa Gelatinase) is a secreted protein which was first purifed, then cloned and sequenced, in 1989 (S.M. Wilhelm et al (1989) J. Biol Chem. 264 (29) : 17213-17221. Published erratum in J. Biol Chem. (1990) 265 (36) : 22570.). A recent review of MMP9 provides an excellent source for detailed information and references on this protease : T.H. Vu & Z. Werb (1998) (In : Matrix Metalloproteinases. 1998. Edited by W.C. Parks & R.P. Mecham. pp115 - 148. Academic Press. ISBN 0-12-545090-7). The following points are drawn from that review by T.H. Vu & Z. Werb (1998).

The expression of MMP9 is restricted normally to a few cell types, including trophoblasts, osteoclasts, neutrophils and macrophages. However, its expression can be induced in these same cells and in other cell types by several mediators, including exposure of the cells to growth factors or cytokines. These are the same mediators often implicated in initiating an inflammatory response. As with other secreted MMPs, MMP9 is released as an inactive pro-enzyme which is subsequently cleaved to form the enzymatically active enzyme. The proteases required for this activation *in vivo* are not known. The balance of active MMP9 versus inactive enzyme is further regulated *in vivo* by interaction with TIMP-1 (Tissue Inhibitor of Metalloproteinases -1), a naturally-occurring protein. TIMP-1 binds to the C-terminal region of MMP9, leading to inhibition of the catalytic domain of MMP9. The balance of induced expression of ProMMP9, cleavage of Pro- to active MMP9 and the presence of TIMP-1 combine to determine the amount of catalytically active MMP9 which is present at a local site. Proteolytically active MMP9 attacks substrates which include gelatin, elastin, and native Type IV and Type V collagens; it has no activity against native Type I collagen, proteoglycans or laminins.

There has been a growing body of data implicating roles for MMP9 in various physiological and pathological processes. Physiological roles include the invasion of embryonic trophoblasts through the uterine epithelium in the early stages of embryonic

implantation; some role in the growth and development of bones; and migration of inflammatory cells from the vasculature into tissues. Increased MMP9 expression has been observed in certain pathological conditions, thereby implicating MMP9 in disease processes such as arthritis, tumour metastasis, Alzheimer's, Multiple Sclerosis, and plaque rupture in atherosclerosis leading to acute coronary conditions such as Myocardial Infarction.

In a first aspect of the invention we provide compounds of the formula I



I

wherein ring B is a monocyclic or bicyclic alkyl, aryl, aralkyl, heteroaryl or heteroaralkyl ring comprising up to 12 ring atoms and containing one or more heteroatoms independently chosen from N, O, and S; alternatively ring B may be biphenyl; ring B may optionally be linked to ring A by a C1-4 alkyl or a C1-4 alkoxy chain linking the 2-position of ring B with a carbon atom alpha to X2;

each R3 is independently selected from hydrogen, halogen, NO2, COOR wherein R is hydrogen or C1-6alkyl, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl ,C1-6 alkoxy and up to C10 aryloxy, n is 1,2 or 3;

P is -(CH_2)n- wherein n = 0, 1, 2, or P is an alkene or alkyne chain of up to six carbon atoms; where X2 is C, P may be -Het-, -(CH[R6])n-Het-, -Het-(CH[R6]n-or -Het-(CH[R6])n-Het-, wherein Het is selected from - CO-, -S-, SO-, -SO2-, -NR6- , or -O- wherein n is 1 or 2, or P may be selected from -CO-N(R6)-, -N(R6)-CO-, -SO2-N(R6)- and -N(R6)-SO2-, and R6 is hydrogen, C1-6 alkyl, up to C10 aralkyl or up to C9 heteroalkyl;

Ring A is a 5-7 membered aliphatic ring and may optionally be mono- or di-substituted by optionally substituted C1-6 alkyl or C1-6 alkoxy, each substituent being independently selected from halogen, C1-6 alkyl or an oxo group;

X1 and X2 are independently selected from N and C, where a ring substituent on ring A is an oxo group this is preferably adjacent a ring nitrogen atom;

Y is selected from -SO2- and -CO-;

Z is -CONHOH , Y is -CO- and Q is selected from -C(R6)(R7)-, -C(R6)(R7)-CH2-, -N(R6)-, and -N(R6)-CH2- wherein R6 is as defined above, and solely in relation to Q as here defined, R6 may also represent up to C10 aryl and up to C9 heteroaryl, and R7 is H, C1-6 alkyl, or together with R6 forms a carbocyclic or heterocyclic spiro 5, 6 or 7 membered ring, the latter containing at least one heteroatom selected from N, O, and S;

Z is -CONHOH, Y is -SO2- and Q is selected from -C(R6)(R7)-, and —C(R6)(R7)-CH2-;

or Z is -N(OH)CHO and Q is selected from -CH(R6)-,-CH(R6)-CH2-, and -N(R6)-CH2-;

R1 is H, or C1-6 alkyl;

Z is selected from -COOH, -CONHOH, -N(OH)CHO and N(OH)COR wherein R is C1-6alkyl, up to C10 aryl and up to C9 aralkyl

and R2 is a heterocyclylalkyl ring having 5-7 ring atoms and comprising one or two ring heteroatoms independently selected from oxygen, nitrogen and sulphur, the ring being optionally substituted by (i) Y-R9 wherein R9 is C1-6 alkyl, up to C10 aryl, up to C12 aralkyl or up to C12 heteroaryl(hetero)alkyl, or (ii) Y-T-R9 wherein Y and R9 are as previously defined and T is oxygen or N-R8 wherein R8 is hydrogen or C1-6alkyl, the heteroatom(s) being independently selected from oxygen, nitrogen and sulphur; R9 and R8 independently being optionally substituted by one or two groups selected from halogen, NO2, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl and C1-6 alkoxy.

Any alkyl groups outlined above may be straight chain or branched.

Convenient values for the above groups include the following:

ring A = a 5-6 membered aliphatic ring, such as a piperazine or piperidine ring, and may optionally be mono- or di-substituted by optionally substituted C1-6 alkyl or C1-6 alkoxy, each substituent being independently selected from halogen, C1-6 alkyl or an oxo group;

R3 = hydrogen, halogen, NO2, CF3, C1-4 alkyl, and C1-4 alkoxy, n is 1 or 2, such as individually 4-fluoro, CF3, 4-chloro and 3,4-dichloro;.

ring B = monocyclic or bicyclic cycloalkyl, aryl, aralkyl or heteroaryl having up to 10 ring atoms, especially monocyclic aryl, aralkyl or heteroaryl having up to 7 ring atoms, more especially monocyclic aryl or heteroaryl having up to 6 ring atoms, such as a phenyl or pyridyl ring;

P = -(CH2)n- wherein n is 0 or 1, or P is -NH-CO-

one or both of X2 and X1 = N

Y = -SO2- or -CO-;

Q = -CH(R6)-, -CH(R6)-CH2-, -N(R6)-, and -N(R6)-CH2- wherein R6 is hydrogen or C1-6 alkyl; when Q = -N(R6)-, or -N(R6)-CH2- then Y may also be -CS-; especially Q= -CH(R6)- wherein R6 is hydrogen or C1-4 alkyl such as propyl or butyl, particularly propyl.; also where Q is linked to R1 or R2 to form a 5-7 alkyl or heteroalkyl ring such as a cyclohexyl ring;

R1 = hydrogen, or C1-4 alkyl.

Z = -CONHOH- or -N(OH)CHO

and R2 is a heterocyclylalkyl ring having 5-7 ring atoms and comprising one or two ring heteroatoms independently selected from oxygen, nitrogen and sulphur, the ring being optionally substituted by (i) Y-R9 wherein R9 is C1-6 alkyl, up to C10 aryl, up to C12 aralkyl or up to C12 heteroaryl(hetero)alkyl, or (ii) Y-T-R9 wherein Y and R9 are as previously defined and T is oxygen or N-R8 wherein R8 is hydrogen or C1-6alkyl, the heteroatom(s) being independently selected from oxygen, nitrogen and sulphur; R9 and R8 independently being optionally substituted by one or two groups selected from halogen, NO2, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl and C1-6 alkoxy.

Preferred values for the above groups include the following:

R3 = hydrogen, chlorine, fluorine, NO2, CF3, methyl, ethyl, methoxy, ethoxy, particularly methoxy or fluorine;

ring B = phenyl, biphenyl, napthyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl, especially phenyl or pyridyl, more especially phenyl or 2-pyridyl;

ring A = piperazine;

P = a direct bond;

both X2 and X1 are N;

Y = -SO2-;

Q = -CH2-;

R2 is a heterocyclylalkyl ring having 5-7 ring atoms and comprising one or two ring heteroatoms independently selected from oxygen, nitrogen and sulphur, the ring being optionally substituted by (i) Y-R9 wherein Y is -SO2- or -CO- and R9 is C1-6 alkyl or alkylamino, up to C10 aryl or arylamino, up to C12 aralkyl or aralkylamino or up to C12 heteroaryl(hetero)alkyl, R9 independently being optionally substituted by one or two groups

selected from halogen, NO2, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl and C1-6 alkoxy;

R1 is hydrogen;

Z is -N(OH)CHO;

More preferred values include:

R3 being methoxy, fluorine or 4-fluoro;

ring A is unsubstituted;

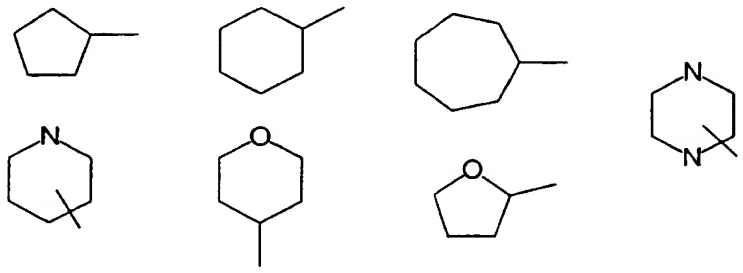
ring B is phenyl, pyridyl, or 2-pyridyl;

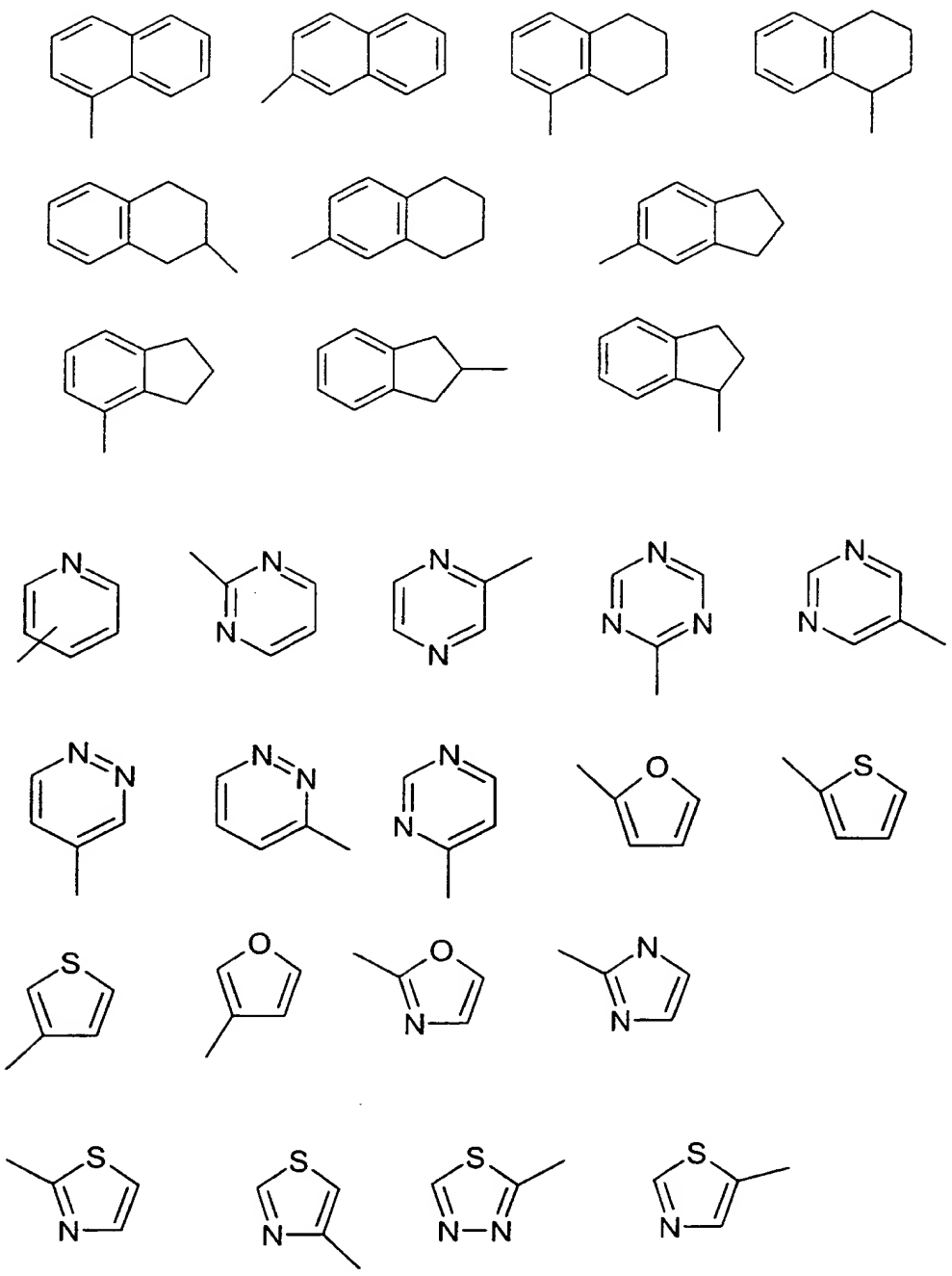
R2 is 3- or 4-piperidinyl, optionally N-substituted by Y-R9 wherein Y is -SO2- or -CO- and R9 is C1-4 alkyl or alkylamino, C6 aryl or arylamino, up to C10 aralkyl or aralkylamino or up to C10 heteroaryl(hetero)alkyl, R9 independently being optionally substituted by one or two groups selected from halogen, CF3, and C1-4 alkyl;

Preferred combinations of Rings A and B include phenyl and piperazinyl; pyridyl and piperazinyl respectively.

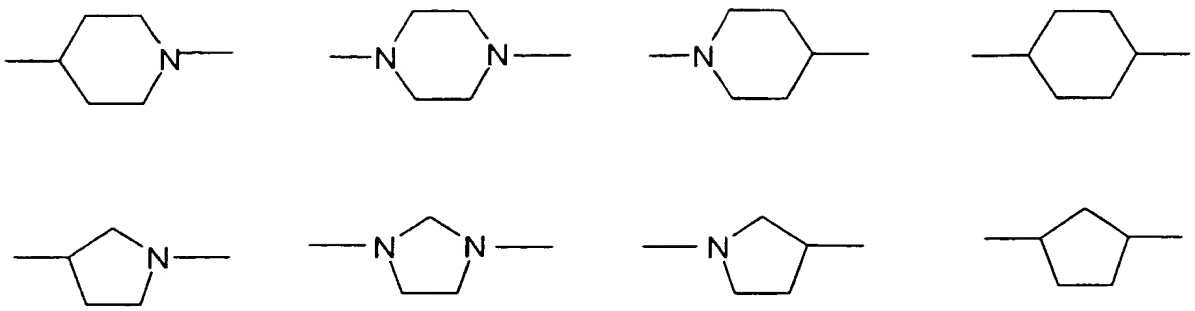
Particular compounds include those where Ring A is unsubstituted.

Particular alicyclic, fused and heterocyclic rings for ring B include any one of





Particular rings for ring A include any one of



and its corresponding seven membered analogue(s).

It will be appreciated that the particular substitituents and number of substituents on rings A and B are selected so as to avoid sterically undesirable combinations.

Where optically active centres exist in the compounds of formula I, we disclose all individual optically active forms and combinations of these as individual specific embodiments of the invention, as well as their corresponding racemates.

The above compounds are potent MMP13 inhbitors, they also have good aggrecanase activity. As previously outlined the compounds of the invention are metalloproteinase inhibitors, in particular they are inhibitors of MMP13. Each of the above indications for the compounds of the formula I represents an independent and particular embodiment of the invention. Whilst we do not wish to be bound by theoretical considerations, the compounds of the invention are believed to show selective inhibition for any one of the above indications relative to any MMP1 inhibitory activity, by way of non-limiting example they may show 100-1000 fold selectivity over any MMP1 inhibitory activity.

The compounds of the invention may be provided as pharmaceutically acceptable salts. These include acid addition salts such as hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine.

They may also be provided as in vivo hydrolysable esters. These are pharmaceutically acceptable esters that hydrolyse in the human body to produce the parent compound. Such esters can be identified by administering, for example intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable in vivo hydrolysable esters for carboxy include methoxymethyl and for hydroxy include acetyl.

In order to use a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically acceptable salt or an in vivo hydrolysable ester and pharmaceutically acceptable carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal adminstration or by inhalation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to hereinabove.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.5 to 75 mg/kg body weight (and preferably of 0.5 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

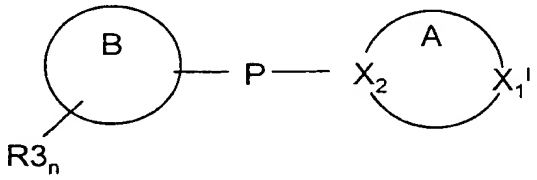
Therefore in a further aspect, the present invention provides a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for use in a method of therapeutic treatment of the human or animal body.

In yet a further aspect the present invention provides a method of treating a metalloproteinase mediated disease condition which comprises administering to a warm-

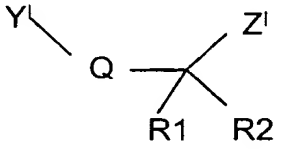
blooded animal a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof.

In another aspect the present invention provides a process for preparing a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof which process comprises

a) reacting a compound of the formula (II) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof with a compound of the formula (III)



II



III

wherein X_1^I represents X or a precursor of X (whether by modification or displacement) or an activated form of X suitable for reaction with Y_1;

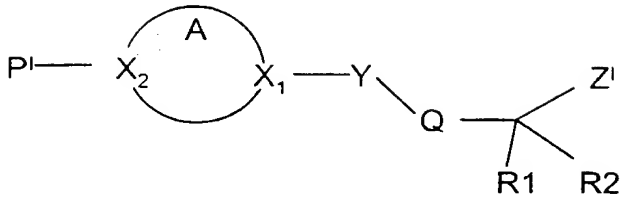
Y_1 represents Y, a precursor of Y, or an activated form of Y suitable for reaction with X_1^I;

by way of non-limiting example, when X is C then X_1 may be derivatised to include a precursor of Y for reaction with a compound of formula III wherein Y^I is a precursor of Y;

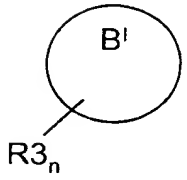
Z^I represents a protected form of Z, a precursor of Z (whether by modification or displacement of Z^I) or an activated form of Z;

or

b) reacting a compound of the formual (IV)) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof with a compound of the formula (V).



IV



V

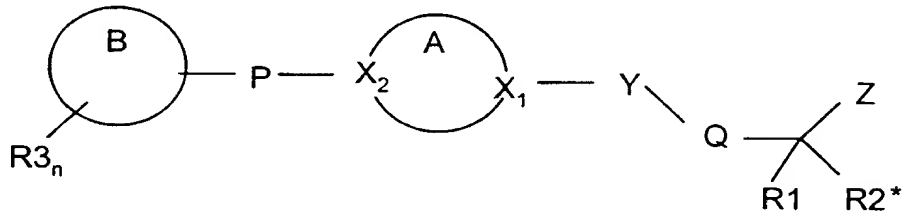
wherein B^I represents a suitable ring function or substituent group for reaction with P^i;

Z^I is as hereinbefore defined; and

P^i represents a suitably activated form of the linker P for reaction with B^I ;

or

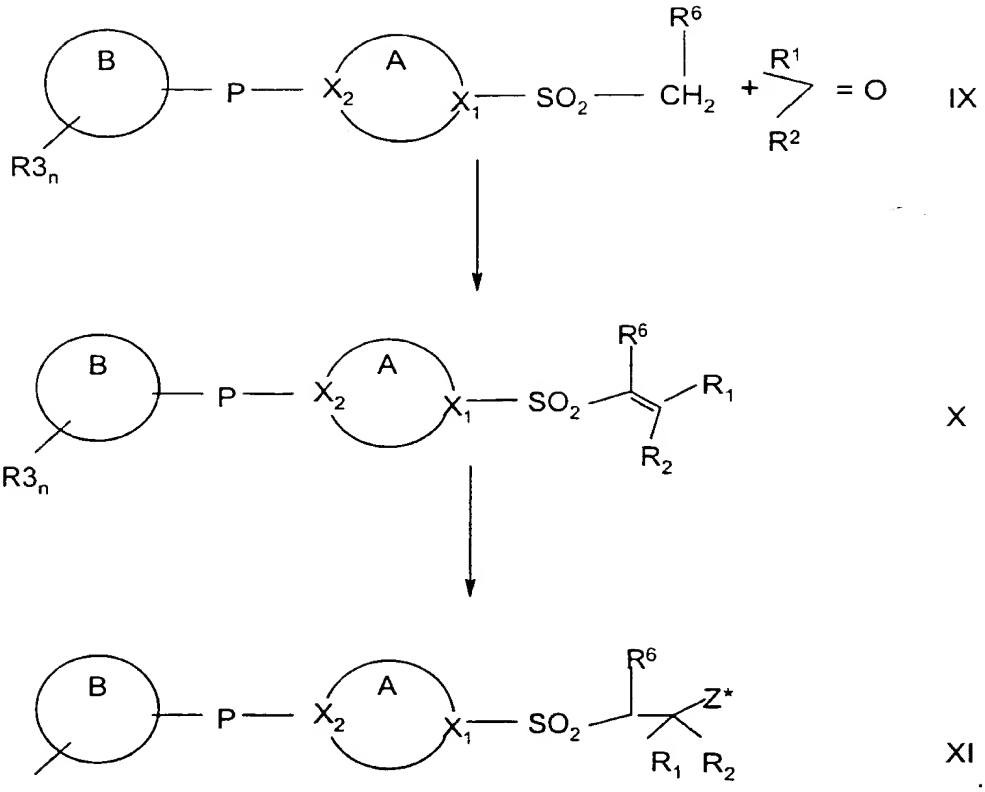
c) reacting a compound of the general formula (VIII)



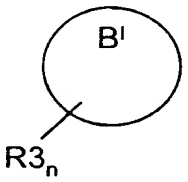
wherein R2* is a precursor for R2 with appropriate reagent(s) in one or more steps to yield R2. The group Z is conveniently protected during such steps. By way of non-limiting example R2* is a piperidine or piperazine ring;

or

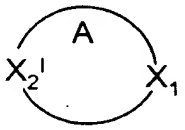
(d) reacting a compound of the formula IX with an appropriate compound of the formula R1-CO-R2 to yield an alkene of the formula X, which is then converted to a compound of the formula XI wherein Z* is a hydroxylamine precursor of the group Z, and then converting Z* to the group Z, all as set out below:



A compound of the formula (II) is conveniently prepared by reacting a compound of the formual (VI) with a compound of the formula (VII)



VI

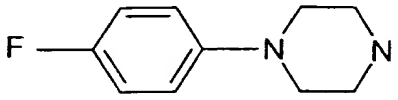


VII

wherein B^I represents a suitable ring function or substituent group, $X_2{}^I$ represents X or a precursor of X (whether by modification or displacement) or an activated form of X suitable for reaction with B^I and wherein B^I and $X_2{}^I$ when reacted together provide the linker P

between ring B and ring A in the compound of formula (II). By way of non-limiting example, when $X_2$is N then ring A is suitably derivatised to introduce the linker P via B^1, and when X_2 is C then both ring A and ring are suitably derivatised to provide the linker P by the reaction of B^1 and X_2^1.

Convenient commercially available starting materials include



The compounds of the invention may be evaluated for example in any one of the following assays:

Isolated Enzyme Assays:

Matrix Metalloproteinase family, including for example MMP13

Recombinant human proMMP13 may be expressed and purified as described by Knauper *et al.* [V. Knauper *et al.*, (1996) The Biochemical Journal 271:1544-1550 (1996)]. The purified enzyme can be used to monitor inhibitors of activity as follows: purified proMMP13 is activated using 1mM amino phenyl mercuric acid (APMA), 20 hours at 21°C; the activated MMP13 (11.25ng per assay) is incubated for 4-5 hours at 35°C in assay buffer (0.1M Tris-HCl, pH 7.5 containing 0.1M NaCl, 20mM $CaCl_2$, 0.02 mM ZnCl and 0.05% (w/v) Brij 35 using the synthetic substrate 7-methoxycoumarin-4-yl)acetyl.Pro.Leu.Gly.Leu.N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl.Ala.Arg.NH_2 in the presence or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 328nm and λem 393nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

A similar protocol can be used for other expressed and purified pro MMPs using substrates and buffers conditions optimal for the particular MMP, for instance as described in C. Graham Knight *et al.*, (1992) FEBS Lett. 296(3):263-266.

Adamalysin family, including for example TNF convertase.

The ability of the compounds to inhibit proTNFα convertase enzyme may be assessed using a partially purified, isolated enzyme assay, the enzyme being obtained from the

membranes of THP-1 as described by K. M. Mohler *et al.*, (1994) Nature 370:218-220. The purified enzyme activity and inhibition thereof is determined by incubating the partially purified enzyme in the presence or absence of test compounds using the substrate 4',5'-Dimethoxy-fluoresceinyl Ser.Pro.Leu.Ala.Gln.Ala.Val.Arg.Ser.Ser.Ser.Arg.Cys(4-(3-succinimid-1-yl)-fluorescein)-NH_2 in assay buffer (50mM Tris HCl, pH 7.4 containing 0.1% (w/v) Triton X-100 and 2mM $CaCl_2$), at 26°C for 18 hours. The amount of inhibition is determined as for MMP13 except λex 490nm and λem 530nm were used. The substrate was synthesised as follows. The peptidic part of the substrate was assembled on Fmoc-NH-Rink-MBHA-polystyrene resin either manually or on an automated peptide synthesiser by standard methods involving the use of Fmoc-amino acids and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) as coupling agent with at least a 4- or 5-fold excess of Fmoc-amino acid and HBTU. Ser^1 and Pro^2 were double-coupled. The following side chain protection strategy was employed; $Ser^1(Bu^t)$, Gln^5(Trityl), $Arg^{8,12}$(Pmc or Pbf), $Ser^{9,10,11}$(Trityl), Cys^{13}(Trityl). Following assembly, the N-terminal Fmoc-protecting group was removed by treating the Fmoc-peptidyl-resin with in DMF. The amino-peptidyl-resin so obtained was acylated by treatment for 1.5-2hr at 70°C with 1.5-2 equivalents of 4',5'-dimethoxy-fluorescein-4(5)-carboxylic acid [Khanna & Ullman, (1980) Anal Biochem. 108:156-161) which had been preactivated with diisopropylcarbodiimide and 1-hydroxybenzotriazole in DMF]. The dimethoxyfluoresceinyl-peptide was then simultaneously deprotected and cleaved from the resin by treatment with trifluoroacetic acid containing 5% each of water and triethylsilane. The dimethoxyfluoresceinyl-peptide was isolated by evaporation, trituration with diethyl ether and filtration. The isolated peptide was reacted with 4-(N-maleimido)-fluorescein in DMF containing diisopropylethylamine, the product purified by RP-HPLC and finally isolated by freeze-drying from aqueous acetic acid. The product was characterised by MALDI-TOF MS and amino acid analysis.

Natural Substrates

The activity of the compounds of the invention as inhibitors of aggrecan degradation may be assayed using methods for example based on the disclosure of E. C. Arner *et al.*, (1998) Osteoarthritis and Cartilage 6:214-228 and the antibodies described therein. The potency of compounds to act as inhibitors against collagenases can be determined as described by T. Cawston and A. Barrett (1979) Anal. Biochem. 99:340-345.

Inhibition of Metalloproteinase Activity in Cell/Tissue Based Activity:

Test as an agent to inhibit membrane sheddases such as TNF convertase

The ability of the compounds of this invention to inhibit the cellular processing of TNFα production may be assessed in THP-1 cells using an ELISA to detect released TNF essentially as described K. M. Mohler *et al.*, (1994) Nature 370:218-220. In a similar fashion the processing or shedding of other membrane molecules such as those described in N. M. Hooper *et al.*, (1997) Biochem. J. 321:265-279 may be tested using appropriate cell lines and with suitable antibodies to detect the shed protein.

Test as an agent to inhibit cell based invasion

The ability of the compound of this invention to inhibit the migration of cells in an invasion assay may be determined as described in A. Albini *et al.*, (1987) Cancer Research 47:3239-3245.

Test as an agent to inhibit whole blood TNF sheddase activity

The ability of the compounds of this invention to inhibit TNFα production is assessed in a human whole blood assay where LPS is used to stimulate the release of TNFα. Heparinized (10Units/ml) human blood obtained from volunteers is diluted 1:5 with medium (RPMI1640 + bicarbonate, penicillin, streptomycin and glutamine) and incubated (160μl) with 20μl of test compound (triplicates), in DMSO or appropriate vehicle, for 30 min at 37°C in a humidified (5%CO_2/95%air) incubator, prior to addition of 20μl LPS (E. coli. 0111:B4; final concentration 10μg/ml). Each assay includes controls of diluted blood incubated with medium alone (6 wells/plate) or a known TNFα inhibitor as standard. The plates are then incubated for 6 hours at 37°C (humidified incubator), centrifuged (2000rpm for 10 min; 4°C), plasma harvested (50-100μl) and stored in 96 well plates at -70°C before subsequent analysis for TNFα concentration by ELISA.

Test as an agent to inhibit in vitro cartilage degradation

The ability of the compounds of this invention to inhibit the degradation of the aggrecan or collagen components of cartilage can be assessed essentially as described by K. M. Bottomley *et al.*, (1997) Biochem J. 323:483-488.

Pharmacodynamic test

To evaluate the clearance properties and bioavailability of the compounds of this invention an ex vivo pharmacodynamic test is employed which utilises the synthetic substrate assays above or alternatively HPLC or Mass spectrometric analysis. This is a generic test

which can be used to estimate the clearance rate of compounds across a range of species. Animals (e.g. rats, marmosets) are dosed iv or po with a soluble formulation of compound (such as 20%w/v DMSO, 60% w/v PEG400) and at subsequent time points (e.g. 5, 15, 30, 60, 120, 240, 480, 720, 1220 mins) the blood samples are taken from an appropriate vessel into 10U heparin. Plasma fractions are obtained following centrifugation and the plasma proteins precipitated with acetonitrile (80%w/v final concentration). After 30 mins at -20°C the plasma proteins are sedimented by centrifugation and the supernatant fraction is evaporated to dryness using a Savant speed vac. The sediment is reconstituted in assay buffer and subsequently analysed for compound content using the synthetic substrate assay. Briefly, a compound concentration-response curve is constructed for the compound undergoing evaluation. Serial dilutions of the reconstituted plasma extracts are assessed for activity and the amount of compound present in the original plasma sample is calculated using the concentration-response curve taking into account the total plasma dilution factor.

In Vivo Assessment

Test as an anti-TNF agent

The ability of the compounds of this invention as *ex vivo* TNFα inhibitors is assessed in the rat. Briefly, groups of male [Wistar Alderley Park (AP)] rats (180-210g) are dosed with compound (6 rats) or drug vehicle (10 rats) by the appropriate route e.g. peroral (p.o.), intraperitoneal (i.p.) , subcutaneous (s.c.). Ninety minutes later rats are sacrificed using a rising concentration of CO_2 and bled out via the posterior vena cavae into 5 Units of sodium heparin/ml blood. Blood samples are immediately placed on ice and centrifuged at 2000 rpm for 10 min at 4°C and the harvested plasmas frozen at -20°C for subsequent assay of their effect on TNFα production by LPS-stimulated human blood. The rat plasma samples are thawed and 175µl of each sample are added to a set format pattern in a 96U well plate. Fifty µl of heparinized human blood is then added to each well, mixed and the plate is incubated for 30 min at 37°C (humidified incubator). LPS (25µl; final concentration10µg/ml) is added to the wells and incubation continued for a further 5.5 hours. Control wells are incubated with 25µl of medium alone. Plates are then centrifuged for 10 min at 2000 rpm and 200µl of the supernatants are transferred to a 96 well plate and frozen at -20°C for subsequent analysis of TNF concentration by ELISA.

Data analysis by dedicated software calculates for each compound/dose:

Percent inhibition of TNFα= $\frac{\text{Mean TNF}\alpha\text{ (Controls) - Mean TNF}\alpha\text{ (Treated) X 100}}{\text{Mean TNF}\alpha\text{ (Controls)}}$

Test as an anti-arthritic agent

Activity of a compound as an anti-arthritic is tested in the collagen-induced arthritis (CIA) as defined by D. E. Trentham *et al.*, (1977) J. Exp. Med. 146,:857. In this model acid soluble native type II collagen causes polyarthritis in rats when administered in Freunds incomplete adjuvant. Similar conditions can be used to induce arthritis in mice and primates.

Test as an anti-cancer agent

Activity of a compound as an anti-cancer agent may be assessed essentially as described in I. J. Fidler (1978) Methods in Cancer Research 15:399-439, using for example the B16 cell line (described in B. Hibner *et al.*, Abstract 283 p75 10th NCI-EORTC Symposium, Amsterdam June 16 - 19 1998).

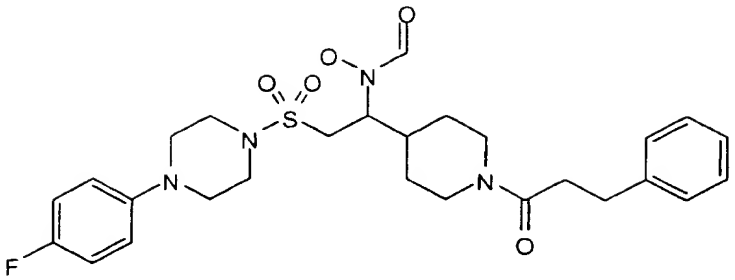
The invention will now be illustrated but not limited by the following Examples:

EXAMPLES

Example 1

Acetic anhydride (1 ml) was added dropwise to formic acid (3 ml) at 0°C and the mixture was stirred at 0°C for 30 minutes. This mixture was added dropwise to a solution of 4-(4-fluorophenyl)-1-[2-(1-phenethylcarbonylpiperidin-4-yl)-2-hydroxylaminoethylsuphonyl]-piperazine (0.65 g) in tetrahydrofuran (5 ml) at 0°C and the mixture was allowed to warm to ambient temperature and was stirred for 10 hours. The reaction mixture was evaporated to small volume, aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate (2x25 ml).

The ethyl acetate extracts were dried and evaporated to dryness. The gum so obtained was subjected to chromatography on silica eluted initially with an ethyl acetate:isohexane mixture (3:2 v/v) and then an ethyl acetate;methanol mixture (9:1). There was obtained **4-(4-fluorophenyl)-1-[2-(1-phenethylcarbonylpiperidin-4-yl)-2-{O-formylhydroxylamino}ethylsuphonyl]-piperazine** as a gum, yield 230 mg, M+H = 547.

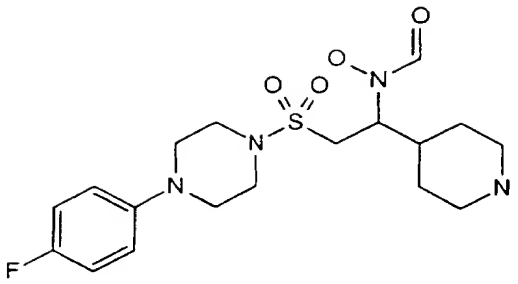


A mixture of 4-(4-fluorophenyl)-1-[2-(1-phenethylcarbonylpiperidin-4-yl)-ethenylsulphonyl]-piperazine (0.75 g) and 50% aqueous hydroxylamine (5 ml) in tetrahydrofuran (10 ml) was stirred for 48 hours. The mixture was evaporated to dryness and water (20 ml) was added. The mixture was extracted with ethyl acetate (2 x 15 ml) and the extracts were washed with water and dried. Removal of the solvent gave 4-(4-fluorophenyl)-1-[2-(1-phenethylcarbonylpiperidin-4-yl)-2-hydroxylaminoethylsuphonyl]-piperazine (0.65 g) as a gum, M+H = 519 (518).

3-Phenylpropionyl chloride (0.21 ml) was added dropwise to a solution of 4-(4-fluorophenyl)-1-[2-(piperidin-4-yl)-ethenylsulphonyl]-piperazine (0.5 g) in dichloromethane containing triethylamine (0.2 ml). The mixture was stirred for 3hours, evaporated to dryness, diluted with water and extracted with ethyl acetate (2 x 15 ml). The ethyl acetate extracts were combined and washed with aqueous sodium bicarbonate, water and dried. Removal of the solvent gave 4-(4-fluorophenyl)-1-[2-(1-phenethylcarbonylpiperidin-4-yl)-ethenylsulphonyl]-piperazine as a gum, M+H = 486 (485).

A mixture of 4-(4-fluorophenyl)-1-[2-(1-t-butoxycarbonylpiperidin-4-yl)-ethenylsulphonyl]-piperazine (1.96 g) and trifluoroacetic acid (5 ml) was stirred at ambient temperature for 5 hours. The mixture was evaporated to dryness, diluted with water, basified with aqueous 2M sodium hydroxide and extracted with ethyl acetate (2 x 20 ml). Removal of the solvent gave 4-(4-fluorophenyl)-1-[2-(piperidin-4-yl)-ethenylsulphonyl]-piperazine.

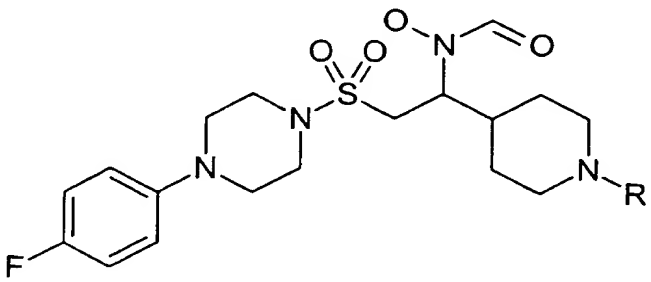
In like manner using 4-(4-fluorophenyl)-1-[2-(1-t-butoxycarbonylpiperidin-4-yl)-2-{O-formylhydroxylamino}ethylsuphonyl]-piperazine as starting material there was obtained 4-(4-fluorophenyl)-1-[2-(piperidin-4-yl)]-2-{O-formylhydroxylamino}ethylsuphonyl]-piperazine, M+H = 415.

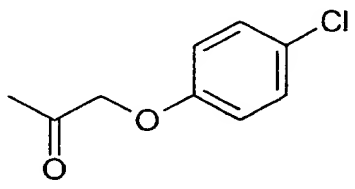


n-Butyl lithium (8.6 ml of a 1.6 M solution in THF) was added dropwise to a suspension of 4-(4-fluorophenyl)-1-methanesulphonylpiperazine (3.52 g) in THF (40 ml) at -78 °C and the mixture was stirred for 30 minutes. Diethylchlorophosphate (1.97 ml) was added dropwise and the mixture was stirred at -78 °C for a further 30 minutes. n-Butyl lithium (8.6 ml of a 1.6 M solution in THF) was added dropwise and stirred for 30 minutes. A solution of 1-(t-butoxycarbonyl)-piperidine-4-aldehyde (2.91 g) in THF (5 ml) was added dropwise and the mixture was allowed to warm to ambient temperature and was stired for 10 hours. Saturated aqueous ammonium chloride solution (5 ml) was added, the reaction mixture was diluted with ethyl acetate (25 ml) and washed with water. Removal of the solvent gave 4-(4-fluorophenyl)-1-[2-(1-t-butoxycarbonylpiperidin-4-yl)-ethenylsulphonyl]-piperazine as a gum which solidified on standing, M+H = 455 (454).

Example 2

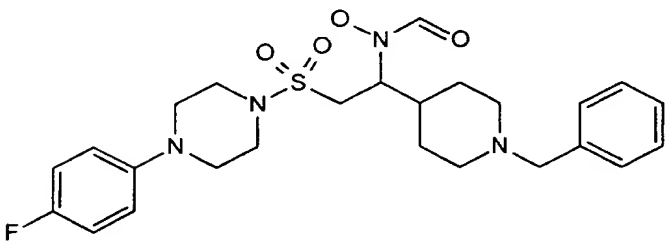
In like manner there were prepared compounds of the formula:

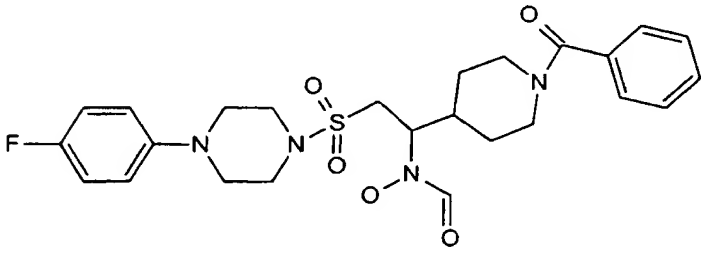


R	M+H
-COOBu^t	515
	583

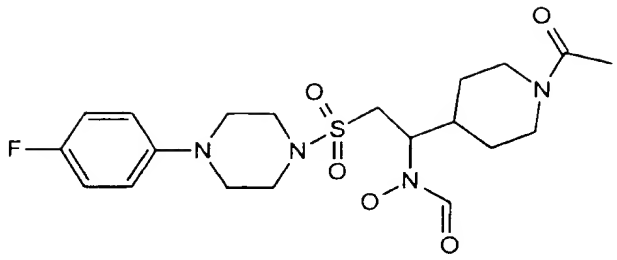
Example 3

Using procedures analogous to those outlined in Example 1 there were prepared:





mpt 132



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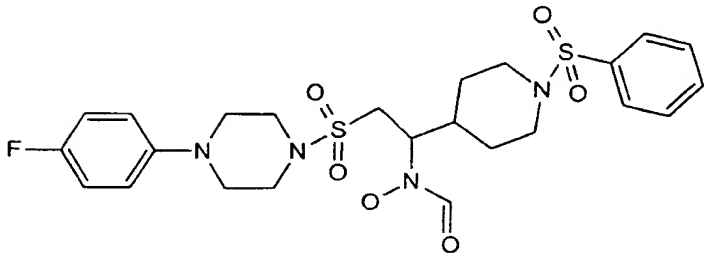
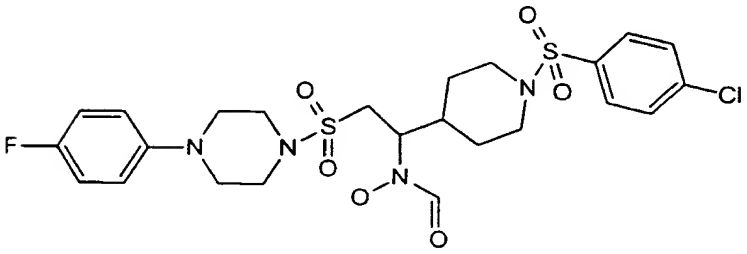
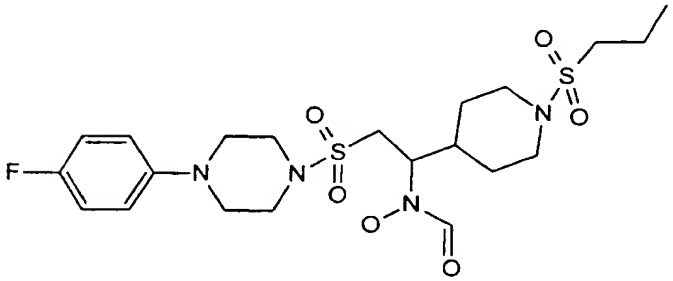


mpt 116-20



mpt 189



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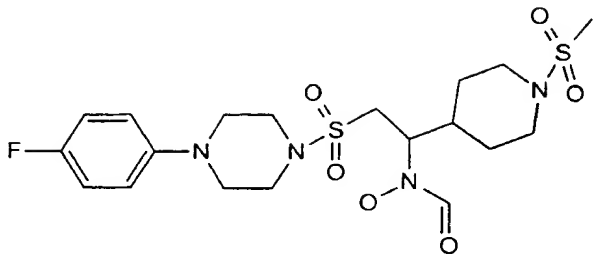

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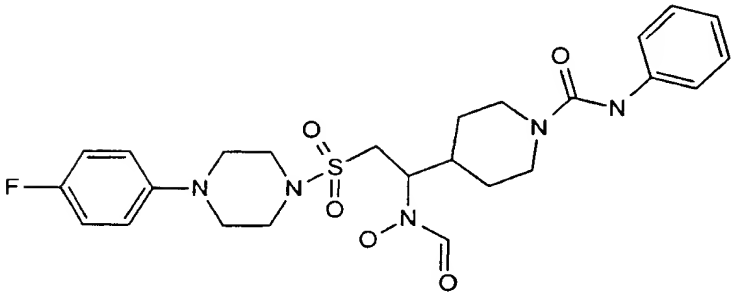
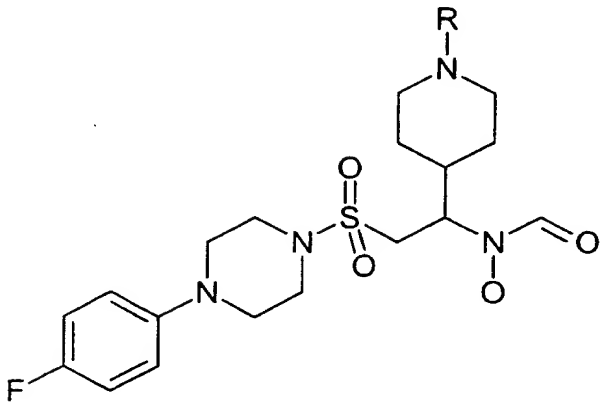
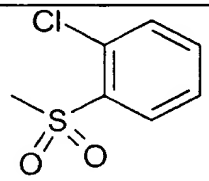
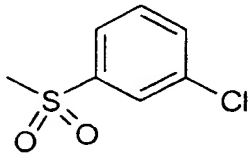
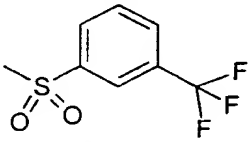
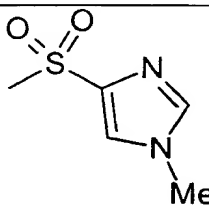
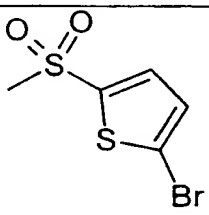
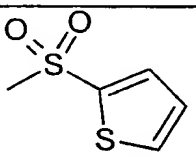
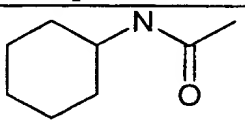


mpt 121

Example 4

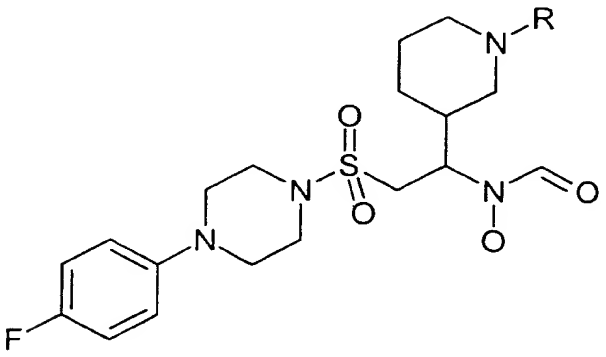
Using procedures analogous to those outlined in Example 1 there were prepared:

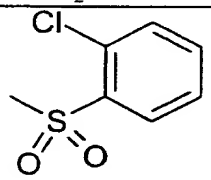
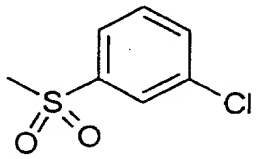
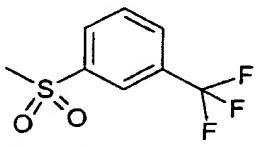
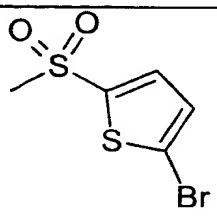
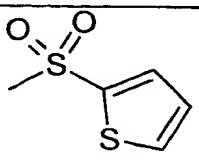


R	MPt °C	M+H
		589
		589
		623
		559
		641
		561
$CF_3CH_2SO_2$-		561
iso-$PrSO_2$-	170-172	
$PhCH_2NHCO$-	130	
	132	
$PhCH_2CH_2NHCO$-	124	
iso-PrNHCO-	155-158	

Example 5

Using procedures analogous to those outlined in Example 1 and using the starting material 1-(t-butoxycarbonyl)-3-formylpiperidine [CAS number 118156-93-7] there were prepared:



R	MPt °C	M+H
PhCO-		519
n-$PrSO_2$-		521
$MeSO_2$-		493
PhNHCO-		534
$PhSO_2$-		555
		589
		589
	108	
	105	
		561
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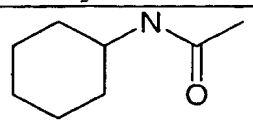
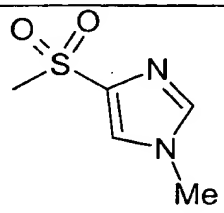
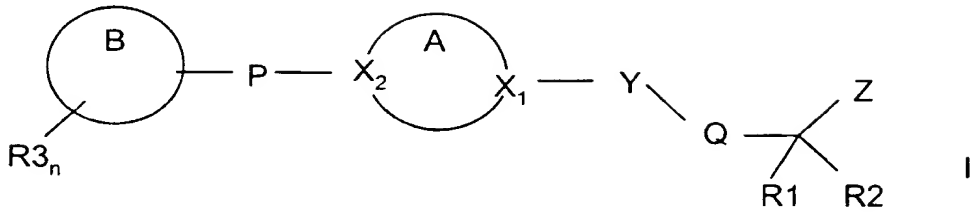
iso-$PrSO_2$-		521
$PhCH_2NHCO$-	95-100	
	110	
$PhCH_2CH_2NHCO$-	90	
iso-PrNHCO-	95-97	
		559

CLAIMS:

What we claim is:-

1. A compound of the formula I



I

wherein ring B is a monocyclic or bicyclic alkyl, aryl, aralkyl, heteroaryl or heteroaralkyl ring comprising up to 12 ring atoms and containing one or more heteroatoms independently chosen from N, O, and S; alternatively ring B may be biphenyl; ring B may optionally be linked to ring A by a C1-4 alkyl or a C1-4 alkoxy chain linking the 2-position of ring B with a carbon atom alpha to X2;

each R3 is independently selected from hydrogen, halogen, NO2, COOR wherein R is hydrogen or C1-6alkyl, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl ,C1-6 alkoxy and up to C10 aryloxy, n is 1,2 or 3;

P is -(CH_2)n- wherein n = 0, 1, 2, or P is an alkene or alkyne chain of up to six carbon atoms; where X2 is C, P may be -Het-, -(CH[R6])n-Het-, -Het-(CH[R6]n-or -Het-(CH[R6])n-Het-, wherein Het is selected from - CO-, -S-, SO-, -SO2-, -NR6- , or -O- wherein n is 1 or 2, or P may be selected from -CO-N(R6)-, -N(R6)-CO-, -SO2-N(R6)- and -N(R6)-SO2-, and R6 is hydrogen, C1-6 alkyl, up to C10 aralkyl or up to C9 heteroalkyl;

Ring A is a 5-7 membered aliphatic ring and may optionally be mono- or di-substituted by optionally substituted C1-6 alkyl or C1-6 alkoxy, each substituent being independently selected from halogen, C1-6 alkyl or an oxo group;

X1 and X2 are independently selected from N and C, where a ring substituent on ring A is an oxo group this is preferably adjacent a ring nitrogen atom;

Y is selected from -SO2- and -CO-;

Z is -CONHOH , Y is -CO- and Q is selected from -C(R6)(R7)-, -C(R6)(R7)-CH2-, -N(R6)-, and -N(R6)-CH2- wherein R6 is as defined above, and solely in relation to Q as here defined, R6 may also represent up to C10 aryl and up to C9 heteroaryl, and R7 is H, C1-6

alkyl, or together with R6 forms a carbocyclic or heterocyclic spiro 5, 6 or 7 membered ring, the latter containing at least one heteroatom selected from N, O, and S;

Z is -CONHOH, Y is -SO2- and Q is selected from -C(R6)(R7)-, and —C(R6)(R7)-CH2-;

or Z is -N(OH)CHO and Q is selected from -CH(R6)-,-CH(R6)-CH2-, and -N(R6)-CH2-;

R1 is H, or C1-6 alkyl;

Z is selected from -COOH, -CONHOH, -N(OH)CHO and N(OH)COR wherein R is C1-6alkyl, up to C10 aryl and up to C9 aralkyl

and R2 is a heterocyclylalkyl ring having 5-7 ring atoms and comprising one or two ring heteroatoms independently selected from oxygen, nitrogen and sulphur, the ring being optionally substituted by (i) Y-R9 wherein R9 is C1-6 alkyl, up to C10 aryl, up to C12 aralkyl or up to C12 heteroaryl(hetero)alkyl, or (ii) Y-T-R9 wherein Y and R9 are as previously defined and T is oxygen or N-R8 wherein R8 is hydrogen or C1-6 alkyl, the heteroatom(s) being independently selected from oxygen, nitrogen and sulphur; R9 and R8 independently being optionally substituted by one or two groups selected from halogen, NO2, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl and C1-6 alkoxy;

or a pharmaceutically-acceptable salt or in vivo hydrolysable precursor thereof.

2. A compound as claimed in claim 1 and wherein:

ring A is a 5-6 membered aliphatic ring and is optionally mono- or di-substituted by optionally substituted C1-6 alkyl or C1-6 alkoxy, each substituent being independently selected from halogen, C1-6 alkyl or an oxo group;

R3 is hydrogen, halogen, NO2, CF3, C1-4 alkyl, and C1-4 alkoxy;

n is 1 or 2;

ring B is monocyclic or bicyclic cycloalkyl, aryl, aralkyl or heteroaryl having up to 10 ring atoms;

P is -(CH2)n- wherein n is 0 or 1, or P is -NH-CO-;

one or both of X2 and X1 = N;

Y is -SO2- or -CO-;

Q is -CH(R6)-, -CH(R6)-CH2-, -N(R6)-, and -N(R6)-CH2- wherein R6 is hydrogen or C1-6 alkyl; when Q = -N(R6)-, or -N(R6)-CH2- then Y may also be -CS-, also Q may be linked to R1 or R2 to form a 5-7 alkyl or heteroalkyl ring;

R1 = hydrogen, or C1-4 alkyl.

Z = -CONHOH- or -N(OH)CHO

and R2 is a heterocyclylalkyl ring having 5-7 ring atoms and comprising one or two ring heteroatoms independently selected from oxygen, nitrogen and sulphur, the ring being optionally substituted by (i) Y-R9 wherein R9 is C1-6 alkyl, up to C10 aryl, up to C12 aralkyl or up to C12 heteroaryl(hetero)alkyl, or (ii) Y-T-R9 wherein Y and R9 are as stated in claim 1 and T is oxygen or N-R8 wherein R8 is hydrogen or C1-6alkyl, the heteroatom(s) being independently selected from oxygen, nitrogen and sulphur; R9 and R8 independently being optionally substituted by one or two groups selected from halogen, NO2, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl and C1-6 alkoxy;

or a pharmaceutically-acceptable salt or in vivo hydrolysable precursor thereof.

3. A compound as claimed in claim 1 and wherein:

R3 is hydrogen, chlorine, fluorine, NO2, CF3, methyl, ethyl, methoxy, ethoxy;

ring B is phenyl, biphenyl, napthyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl;

P is a direct bond;

both X2 and X1 are N;

Y is -SO2-;

Q is -CH2-;

R2 is a heterocyclylalkyl ring having 5-7 ring atoms and comprising one or two ring heteroatoms independently selected from oxygen, nitrogen and sulphur, the ring being optionally substituted by (i) Y-R9 wherein Y is as stated in claim 1 and R9 is C1-6 alkyl or alkylamino, up to C10 aryl or arylamino, up to C12 aralkyl or aralkylamino, up to C12 heteroaryl(hetero)alkyl, R9 independently being optionally substituted by one or two groups selected from halogen, NO2, CN, CF3, C1-6 alkyl, -S-C1-6 alkyl, -SO-C1-6 alkyl, -SO2-C1-6 alkyl and C1-6 alkoxy;

R1 is hydrogen;

Z is -N(OH)CHO;

or a pharmaceutically-acceptable salt or in vivo hydrolysable precursor thereof.

4. A compound as claimed in claim 1 and wherein:

R3 is methoxy, fluorine or 4-fluoro;

ring A is unsubsituted;

ring B is phenyl, pyridyl, or 2-pyridyl;

R2 is optionally substituted 3-piperidinyl, 4-piperidinyl or N-substituted 4-piperidinyl, wherein the substituents are as stated in claim 3;

or a pharmaceutically-acceptable salt or in vivo hydrolysable precursor thereof.

5. A compound as claimed in claim 1 and wherein R2 is 3- or 4-piperidinyl, optionally N-substituted by Y-R9 wherein Y is as stated in claim 1 and R9 is C1-4 alkyl or alkylamino, C6 aryl or arylamino, up to C10 aralkyl or aralkylamino or up to C10 heteroaryl(hetero)alkyl, R9 independently being optionally substituted by one or two groups selected from halogen, CF3, and C1-4 alkyl;

or a pharmaceutically-acceptable salt or in vivo hydrolysable precursor thereof.

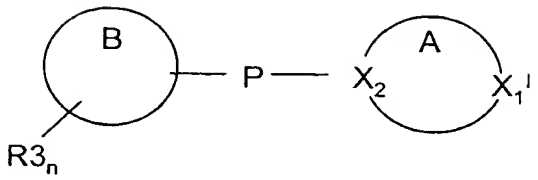
6. A pharmaceutical composition which comprises a compound of the formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt or an in vivo hydrolysable ester and a pharmaceutically acceptable carrier.

7. A compound of the formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for use in a method of therapeutic treatment of the human or animal body.

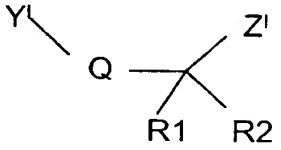
8. A method of treating a metalloproteinase mediated disease condition which comprises administering to a warm-blooded animal a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof.

9. A process for preparing a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof which process comprises

a) reacting a compound of the formula (II) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof with a compound of the formula (III)



II



III

wherein X_1^I represents X or a precursor of X (whether by modification or displacement) or an activated form of X suitable for reaction with Y_1;

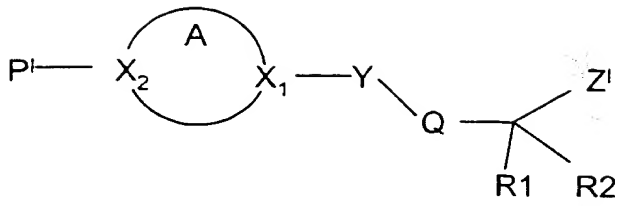
Y_1 represents Y, a precursor of Y, or an activated form of Y suitable for reaction with X_1^I;

by way of non-limiting example, when X is C then X_1 may be derivatised to include a precursor of Y for reaction with a compound of formula III wherein Y^I is a precursor of Y;

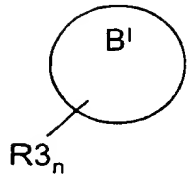
Z^I represents a protected form of Z, a precursor of Z (whether by modification or displacement of Z^I) or an activated form of Z;

or

b) reacting a compound of the formual (IV)) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof with a compound of the formula (V).



IV



V

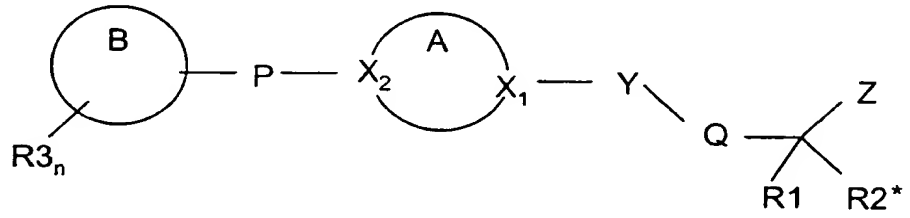
wherein B^I represents a suitable ring function or substituent group for reaction with P^i;

Z^I is as hereinbefore defined; and

P^i represents a suitably activated form of the linker P for reaction with A^I;

or

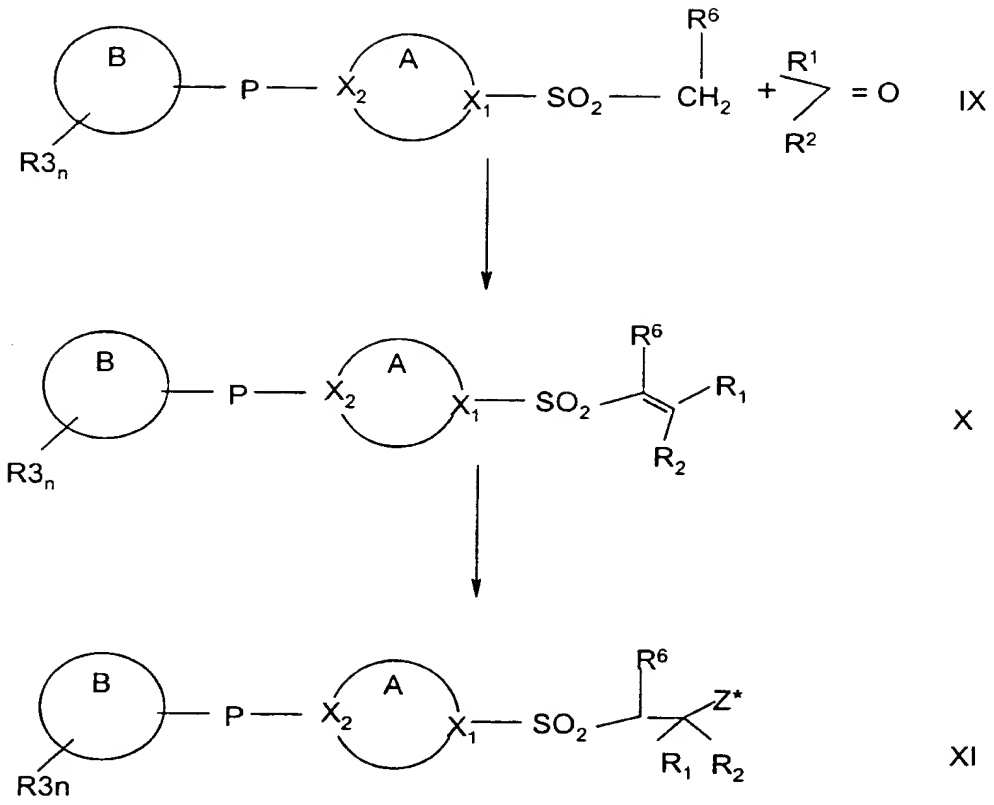
c) reacting a compound of the general formula (VIII)



wherein R2* is a precursor for R2 with appropriate reagent(s) in one or more steps to yield R2. The group Z is conveniently protected during such steps. By way of non-limiting example R2* is a piperidine or piperazine ring;

or

(d) reacting a compound of the formula IX with an appropriate compound of the formula R1-CO-R2 to yield an alkene of the formula X, which is then converted to a compound of the formula XI wherein Z* is a hydroxylamine precursor of the group Z, and then converting Z* to the group Z, all as set out below:



10. The use of a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable precursor thereof in the preparation of a medicament for use in a disease condition mediated by one or more metalloproteinase enzymes.

11. The use of a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable precursor thereof in the preparation of a medicament for use in the treatment of arthritis.

12. The use of a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable precursor thereof in the preparation of a medicament for use in the treatment of atherosclerosis.

INTERNATIO SEARCH REPORT

Inte. .onal Application No
PCT/GB 00/02085

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/28 C07D401/12 C07D409/12 A61K31/445 A61K31/4535 A61P19/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 02510 A (BISSOLINO PIERLUIGI ;JABES DANIELA (IT); ALPEGIANI MARCO (IT); PER) 21 January 1999 (1999-01-21) claim 1; examples	1-12
A	US 5 817 822 A (MACPHERSON LAWRENCE J ET AL) 6 October 1998 (1998-10-06) claim 1	1-12
A	DE 198 02 350 A (HOFFMANN LA ROCHE ;AGOURON PHARMA (US)) 30 July 1998 (1998-07-30) claim 1; examples	1-12
A	WO 99 18074 A (DU PONT PHARM CO) 15 April 1999 (1999-04-15) claim 1; examples	1-12

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2000	24/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 12478 A (ZENECA PHARMA SA ;TUCKER HOWARD (GB); WATERSON DAVID (GB); ZENECA) 9 March 2000 (2000-03-09) compound in which R1 is N-PhCH2-4-piperidinyl page 42	1-12
P,X	WO 99 38843 A (DARWIN DISCOVERY LTD) 5 August 1999 (1999-08-05) claims; examples	1,6-8, 10-12

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,4-12 (all partially)

Present claims 1,4-12 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I, in which Z is -CONHOH, -N(OH)CHO or -N(OH)COR.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/02085

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		NO 20000783 A	29-05-2000
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WO 9938843 A	05-08-1999	AU 2291499 A	16-08-1999
		NO 20003868 A	28-07-2000

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 December 2000 (14.12.2000)

PCT

(10) International Publication Number
WO 00/75108 A1

(51) International Patent Classification[7]: C07D 211/28, 401/12, 409/12, A61K 31/445, 31/4535, A61P 19/02

(21) International Application Number: PCT/GB00/02085

(22) International Filing Date: 31 May 2000 (31.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99401350.6 4 June 1999 (04.06.1999) EP

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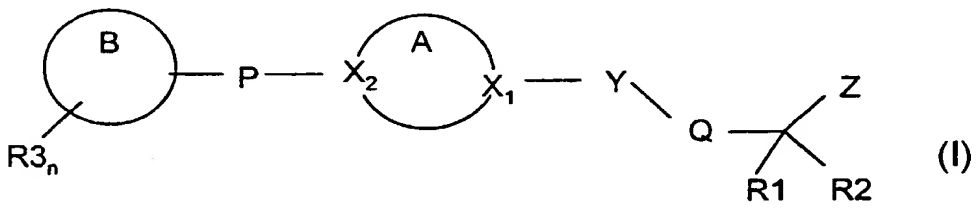
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INHIBITORS OF METALLOPROTEINASES



(I)

(57) Abstract: Arylpiperazines of formula (I) having a heterocyclylalkyl substituent at R2, useful as metalloproteinase inhibitors, especially useful as MMP13 inhibitors.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organizati n
International Bureau

(43) International Publication Date
14 December 2000 (14.12.2000)

PCT

(10) International Publication Number
WO 00/75108 A1

(51) International Patent Classification[7]: C07D 211/28, 401/12, 409/12, A61K 31/445, 31/4535, A61P 19/02

(21) International Application Number: PCT/GB00/02085

(22) International Filing Date: 31 May 2000 (31.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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Published:
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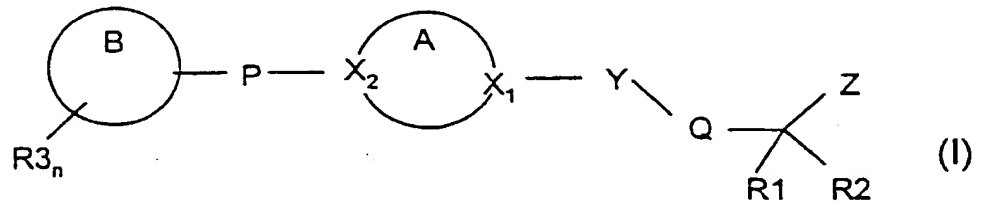

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WO 00/75108 A1